ZITERA®

Levetiracetam film-coated tablets

DRUG DESCRIPTION

Zitera® is an antiepileptic drug available as 500 mg yellow film-coated tablets and 1000 mg white film-coated tablets.
Zitera® tablets contain the labeled amount of Levetiracetam.
Inactive ingredients: Pregelatinized corn starch, povidone, L-Hydroxypropylcellulose, colloidal silicon dioxide, crospovidone and magnesium stearate.
The film coating solution contains:
500 mg tablets: Yellow iron oxide, quinoline yellow aluminum lake, lecithin, polyethylene glycol 3350, polyvinyl alcohol, talc and titanium dioxide.
1000 mg tablets: Polyvinyl alcohol, titanium dioxide, talc, polyethylene glycol 3350 and lecithin.

INDICATIONS

Zitera® is indicated as adjunctive therapy in the treatment of partial onset seizures in adults and children 4 years of age and older with epilepsy.
Zitera® is indicated as adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents 12 years of age and older with juvenile myoclonic epilepsy.
Zitera® is indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children 6 years of age and older with idiopathic generalized epilepsy.

DOSAGE AND ADMINISTRATION

Partial Onset Seizures

Adults 16 Years and Older

In clinical trials, daily doses of 1000 mg, 2000 mg and 3000 mg, given as twice-daily dosing, were shown to be effective. Although in some studies there was a tendency toward greater response with higher dose, a consistent increase in response with increased dose has not been shown.
Treatment should be initiated with a daily dose of 1000 mg, given as twice-daily dosing (500 mg BID). Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg. Doses greater than 3000 mg/day have been used in open-label studies for periods of 6 months and longer. There is no evidence that doses greater than 3000 mg/day confer additional benefit.

Pediatric Patients Ages 4 to < 16 Years

Treatment should be initiated with a daily dose of 20 mg/kg in 2 divided doses (10 mg/kg BID). The daily dose should be increased every 2 weeks by increments of 20 mg/kg to the recommended daily dose of 60 mg/kg (30 mg/kg BID). If a patient cannot tolerate a daily dose of 60 mg/kg, the daily dose may be reduced. In the clinical trial, the mean daily dose was 52 mg/kg. Patients with body weight above 20 kg can be dosed with tablets (see Table 1).

Table 1: Zitera Tablet Weight-Based Dosing Guide for Children

Patient Weight	Daily Dose		
	20 mg/Kg/day (BID dosing)	40 mg/Kg/day (BID dosing)	60 mg/Kg/day (BID dosing)
20.1 - 40 Kg	500 mg/day (1 x 250 mg tablet BID)	1000 mg/day (1 x 500 mg tablet BID)	1500 mg/day (1 x 750 mg tablet BID)
> 40 Kg	1000 mg/day (1 x 500 mg tablet BID)	2000 mg/day (2 x 500 mg tablets BID)	3000 mg/day (2 x 750 mg tablets BID)

Zitera® is given orally with or without food.

Myoclonic Seizures In Patients 12 Years Of Age And Older With Juvenile Myoclonic Epilepsy

Treatment should be initiated with a dose of 1000 mg/day, given as twice-daily dosing (500 mg BID). Dosage should be increased by 1000 mg/day every 2 weeks to the recommended daily dose of 3000 mg. The effectiveness of doses lower than 3000 mg/day has not been studied.

Primary Generalized Tonic-Clonic Seizures

Adults 16 Years and Older

Treatment should be initiated with a dose of 1000 mg/day, given as twice-daily dosing (500 mg BID). Dosage should be increased by 1000 mg/day every 2 weeks to the recommended daily dose of 3000 mg. The effectiveness of doses lower than 3000 mg/day has not been adequately studied.

Pediatric Patients Ages 6 to < 16 Years

Treatment should be initiated with a daily dose of 20 mg/kg in 2 divided doses (10 mg/kg BID). The daily dose should be increased every 2 weeks by increments of 20 mg/kg to the recommended daily dose of 60 mg/kg (30 mg/kg BID). The effectiveness of doses lower than 60 mg/kg/day has not been adequately studied. Patients with body weight above 20 kg can be dosed with tablets (see Table 1).

Adult Patients With Impaired Renal Function

Zitera® dosing must be individualized according to the patient's renal function status. Recommended doses and adjustment for dose for adults are shown in the table below. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in mL/min is needed.

Table 2: Dosing Adjustment Regimen For Adult Patients With Impaired Renal Function

Group	Creatinine Clearance (mL/min)	Dosage (mg)	Frequency
Normal	> 80	500 to 1,500	Every 12 h
Mild	50 – 80	500 to 1,000	Every 12 h
Moderate	30 – 50	250 to 750	Every 12 h
Severe	< 30	250 to 500	Every 12 h
ESRD patients using dialysis	----	500 to 1,000	Every 24 h*

*Following dialysis, a 250 to 500 mg supplemental dose is recommended.

SIDE EFFECTS

The prescriber should be aware that the adverse event incidence figures in the following tables, obtained when Levetiracetam was added to concurrent AED therapy, cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

Partial Onset Seizures

In well-controlled clinical studies in adults with partial onset seizures, the most frequently reported adverse events associated with the use of Levetiracetam in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, asthenia, infection and dizziness. In the well-controlled pediatric clinical study in children 4 to 16 years of age with partial onset seizures, the adverse events most frequently reported with the use of Levetiracetam in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, accidental injury, hostility, nervousness and asthenia.

Table 3 lists treatment-emergent adverse events that occurred in at least 1% of adult epilepsy patients treated with Levetiracetam participating in placebo-controlled studies and were numerically more common than in patients treated with placebo. Table 4 lists treatment-emergent adverse events that occurred in at least 2% of pediatric epilepsy patients (ages 4-16 years) treated with Levetiracetam participating in the placebo-controlled study and were numerically more common than in pediatric patients treated with placebo. In these studies, either Levetiracetam or placebo was added to concurrent AED therapy. Adverse events were usually mild to moderate in intensity.

Table 3: Incidence (%) Of Treatment-Emergent Adverse Events In Placebo-Controlled, Add-On Studies In Adults Experiencing Partial Onset Seizures By Body System (Adverse Events Occurred In At Least 1% Of Levetiracetam-Treated Patients And Occurred More Frequently Than Placebo-Treated Patients)

Body System/Adverse Event	Levetiracetam (N=769) %	Placebo (N=439) %
Body as a Whole		
Asthenia	15	9
Headache	14	13
Infection	13	8
Pain	7	6
Digestive System		
Anorexia	3	2
Nervous System		
Somnolence	15	8
Dizziness	9	4
Depression	4	2
Nervousness	4	2
Ataxia	3	1
Vertigo	3	1
Amnesia	2	1
Anxiety	2	1
Hostility	2	1
Paresthesia	2	1
Emotional Lability	2	0
Respiratory System		
Pharyngitis	6	4
Rhinitis	4	3
Cough Increased	2	1
Sinusitis	2	1
Special Senses		
Diplopia	2	1

Other events reported by at least 1% of adult Levetiracetam-treated patients but as or more frequent in the placebo group were the following: abdominal pain, accidental injury , amblyopia, arthralgia, back pain, bronchitis, chest pain, confusion, constipation, convulsion, diarrhea, drug level increased, dyspepsia, ecchymosis, fever, flu syndrome, fungal infection, gastroenteritis, gingivitis, grand mal convulsion, insomnia, nausea, otitis media, rash, thinking abnormal, tremor, urinary tract infection, vomiting and weight gain.

Table 4: Incidence (%) Of Treatment-Emergent Adverse Events In A Placebo-Controlled, Add-On Study In Pediatric Patients Ages 4-16 Years Experiencing Partial Onset Seizures By Body System (Adverse Events Occurred In At Least 2% Of Levetiracetam-Treated Patients And Occurred More Frequently Than Placebo-Treated Patients)

Body System / Adverse Event	Levetiracetam (N=101) %	Placebo (N=97) %
Body as a Whole		
Accidental Injury	17	10
Asthenia	9	3
Pain	6	3
Flu Syndrome	3	2
Face Edema	2	1
Neck Pain	2	1
Viral Infection	2	1
Digestive System		
Vomiting	15	13
Anorexia	13	8
Diarrhea	8	7
Gastroenteritis	4	2
Constipation	3	1
Hemic and Lymphatic System		
Ecchymosis	4	1
Metabolic and Nutritional		
Dehydration	2	1
Nervous System		
Somnolence	23	11
Hostility	12	6
Nervousness	10	2
Personality Disorder	8	7
Dizziness	7	2
Emotional Lability	6	4
Agitation	6	1
Depression	3	1
Vertigo	3	1
Reflexes Increased	2	1
Confusion	2	0
Respiratory System		
Rhinitis	13	8
Cough Increased	11	7
Pharyngitis	10	8
Asthma	2	1
Skin and Appendages		
Pruritus	2	0
Skin Discoloration	2	0
Vesiculobullous Rash	2	0
Special Senses		
Conjunctivitis	3	2
Amblyopia	2	0
Ear Pain	2	0
Urogenital System		
Albuminuria	4	0
Urine Abnormality	2	1

Other events occurring in at least 2% of pediatric Levetiracetam-treated patients but as or more frequent in the placebo group were the following: abdominal pain, allergic reaction, ataxia, convulsion, epistaxis, fever, headache, hyperkinesia, infection, insomnia, nausea, otitis media, rash, sinusitis, status epilepticus (not otherwise specified), thinking abnormal, tremor and urinary incontinence.

Myoclonic Seizures

Although the pattern of adverse events in this study seems somewhat different from that seen in patients with partial seizures, this is likely due to the much smaller number of patients in this study compared to partial seizure studies. The adverse event pattern for patients with JME is expected to be essentially the same as for patients with partial seizures.
In the well-controlled clinical study that included both adolescent (12 to 16 years of age) and adult patients with myoclonic seizures, the most frequently reported adverse events associated with the use of Levetiracetam in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, neck pain and pharyngitis.
Table 5 lists treatment-emergent adverse events that occurred in at least 5% of juvenile myoclonic epilepsy patients experiencing myoclonic seizures treated with Levetiracetam and were numerically more common than in patients treated with placebo. In this study, either Levetiracetam or placebo was added to concurrent AED therapy. Adverse events were usually mild to moderate in intensity.

Table 5: Incidence (%) Of Treatment-Emergent Adverse Events In A Placebo-Controlled, Add-On Study In Patients 12 Years Of Age And Older With Myoclonic Seizures By Body System (Adverse Events Occurred In At Least 5% Of Levetiracetam-Treated Patients And Occurred More Frequently Than Placebo-Treated Patients)

Body System/ MedDRA preferred term	Levetiracetam (N=60) %	Placebo (N=60) %
Ear and labyrinth disorders		
Vertigo	5	3
Infections and infestations		
Pharyngitis	7	0
Influenza	5	2
Musculoskeletal and connective tissue disorders		
Neck pain	8	2
Nervous system disorders		
Somnolence	12	2
Psychiatric disorders		
Depression	5	2

Other events occurring in at least 5% of Levetiracetam-treated patients with myoclonic seizures but as or more frequent in the placebo group were the following: fatigue and headache.

Primary Generalized Tonic-Clonic Seizures

Although the pattern of adverse events in this study seems somewhat different from that seen in patients with partial seizures, this is likely due to the much smaller number of patients in this study compared to partial seizure studies. The adverse event pattern for patients with PGTC seizures is expected to be essentially the same as for patients with partial seizures. In the well-controlled clinical study that included patients 4 years of age and older with primary generalized tonic-clonic (PGTC) seizures, the most frequently reported adverse event associated with the use of Levetiracetam in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, was nasopharyngitis.
Table 6 lists treatment-emergent adverse events that occurred in at least 5% of idiopathic generalized epilepsy patients experiencing PGTC seizures treated with Levetiracetam and were numerically more common than in patients treated with placebo. In this study, either Levetiracetam or placebo was added to concurrent AED therapy. Adverse events were usually mild to moderate in intensity.

Table 6: Incidence (%) Of Treatment-Emergent Adverse Events In A Placebo-Controlled, Add-On Study In Patients 4 Years Of Age And Older With PGTC Seizures By MedDRA System Organ Class (Adverse Events Occurred In At Least 5% Of Levetiracetam-Treated Patients And Occurred More Frequently Than Placebo-Treated Patients)

MedDRA System Organ Class/ Preferred Term	Levetiracetam (N=79) %	Placebo (N=84) %
Gastrointestinal disorders		
Diarrhea	8	7
General disorders and administration site conditions		
Fatigue	10	8
Infections and infestations		
Nasopharyngitis	14	5
Psychiatric disorders		
Irritability	6	2
Mood swings	5	1

Other events occurring in at least 5% of Levetiracetam-treated patients with PGTC seizures but as or more frequent in the placebo group were the following: dizziness, headache, influenza and somnolence.

Time Course Of Onset Of Adverse Events For Partial Onset Seizures

Of the most frequently reported adverse events in adults experiencing partial onset seizures, asthenia, somnolence and dizziness appeared to occur predominantly during the first 4 weeks of treatment with Levetiracetam.

Discontinuation Or Dose Reduction In Well-Controlled Clinical Studies

Partial Onset Seizures

In well-controlled adult clinical studies, 15.0% of patients receiving Levetiracetam and 11.6% receiving placebo either discontinued or had a dose reduction as a result of an adverse event. Table 7 lists the most common (> 1%) adverse events that resulted in discontinuation or dose reduction.

Table 7: Adverse Events That Most Commonly Resulted In Discontinuation Or Dose Reduction In Placebo-Controlled Studies In Adult Patients Experiencing Partial Onset Seizures

	Number (%)	
	Levetiracetam (N=769)	Placebo (N=439)
Asthenia	10 (1.3%)	3 (0.7%)
Convulsion	23 (3.0%)	15 (3.4%)
Dizziness	11 (1.4%)	0
Rash	0	5 (1.1%)
Somnolence	34 (4.4%)	7 (1.6%)

In the well-controlled pediatric clinical study, 16.8% of patients receiving Levetiracetam and 20.6% receiving placebo either discontinued or had a dose reduction as a result of an adverse event. The adverse events most commonly associated (≥ 3% in patients receiving Levetiracetam) with discontinuation or dose reduction in the well-controlled study are presented in Table 8.

Table 8: Adverse Events Most Commonly Associated With Discontinuation Or Dose Reduction In The Placebo-Controlled Study In Pediatric Patients Ages 4-16 Years Experiencing Partial Onset Seizures

	Number (%)	
	Levetiracetam (N=101)	Placebo (N=97)
Asthenia	3 (3.0%)	0
Hostility	7 (6.9%)	2 (2.1%)
Somnolence	3 (3.0%)	3 (3.1%)

Myoclonic Seizures

In the placebo-controlled study, 8.3% of patients receiving Levetiracetam and 1.7% receiving placebo either discontinued or had a dose reduction as a result of an adverse event. The adverse events that led to discontinuation or dose reduction in the well-controlled study are presented in Table 9.

Table 9: Adverse Events That Resulted In Discontinuation Or Dose Reduction In The Placebo-Controlled Study In Patients With Juvenile Myoclonic Epilepsy

Body System/ MedDRA preferred term	Levetiracetam (N=60) n (%)	Placebo (N=60) n (%)
Anxiety	2 (3.3%)	1 (1.7%)
Depressed mood	1 (1.7%)	0
Depression	1 (1.7%)	0
Diplopia	1 (1.7%)	0
Hypersomnia	1 (1.7%)	0
Insomnia	1 (1.7%)	0
Irritability	1 (1.7%)	0
Nervousness	1 (1.7%)	0
Somnolence	1 (1.7%)	0

Primary Generalized Tonic-Clonic Seizures

In the placebo-controlled study, 5.1% of patients receiving Levetiracetam and 8.3% receiving placebo either discontinued or had a dose reduction during the treatment period as a result of a treatment-emergent adverse event.
This study was too small to adequately characterize the adverse events leading to discontinuation. It is expected that the adverse events that would lead to discontinuation in this population would be similar to those resulting in discontinuation in other epilepsy trials.

Comparison Of Gender

The overall adverse experience profile of Levetiracetam was similar between females and males.

Postmarketing Experience

In addition to the adverse experiences listed above, the following have been reported in patients receiving marketed Levetiracetam worldwide. The listing is alphabetized: abnormal liver function test, hepatic failure, hepatitis, leukopenia, neutropenia, pancreatitis, pancytopenia (with bone marrow suppression identified in some of these cases), thrombocytopenia and weight loss. Alopecia has been reported with Levetiracetam use; recovery was observed in majority of cases where Levetiracetam was discontinued. These adverse experiences have not been listed above and data are insufficient to support an estimate of their incidence or to establish causation.

Drug Abuse And Dependence

The abuse and dependence potential of Levetiracetam has not been evaluated in human studies.

DRUG INTERACTIONS

In vitro data on metabolic interactions indicate that Levetiracetam is unlikely to produce, or be subject to, pharmacokinetic interactions. Levetiracetam and its major metabolite, at concentrations well above Cmax levels achieved within the therapeutic dose range, are neither inhibitors of nor high affinity substrates for human liver cytochrome P450 isoforms, epoxide hydrolase or UDP-glucuronidation enzymes. In addition, Levetiracetam does not affect the *in vitro* glucuronidation of valproic acid. Levetiracetam circulates largely unbound (< 10% bound) to plasma proteins; clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely.
Potential pharmacokinetic interactions were assessed in clinical pharmacokinetic studies (phenytoin, valproate, oral contraceptive, digoxin,

warfarin, probenecid) and through pharmacokinetic screening in the placebo-controlled clinical studies in epilepsy patients.

Drug-Drug Interactions Between Levetiracetam And Other Antiepileptic Drugs (AEDs)

Phenytoin

Levetiracetam (3000 mg daily) had no effect on the pharmacokinetic disposition of phenytoin in patients with refractory epilepsy. Pharmacokinetics of Levetiracetam were also not affected by phenytoin.

Valproate

Levetiracetam (1500 mg twice daily) did not alter the pharmacokinetics of valproate in healthy volunteers. Valproate 500 mg twice daily did not modify the rate or extent of Levetiracetam absorption or its plasma clearance or urinary excretion.

Potential drug interactions between Levetiracetam and other AEDs (carbamazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone and valproate) were also assessed by evaluating the serum concentrations of Levetiracetam and these AEDs during placebo-controlled clinical studies. These data indicate that Levetiracetam does not influence the plasma concentration of other AEDs and that these AEDs do not influence the pharmacokinetics of Levetiracetam.

Effect Of AEDs In Pediatric Patients

There was about a 22% increase of apparent total body clearance of Levetiracetam when it was co-administered with enzyme-inducing AEDs. Dose adjustment is not recommended. Levetiracetam had no effect on plasma concentrations of carbamazepine, valproate, topiramate or lamotrigine.

Other Drug Interactions

Oral Contraceptives

Levetiracetam (500 mg twice daily) did not influence the pharmacokinetics of an oral contraceptive containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel, or of the luteinizing hormone and progesterone levels, indicating that impairment of contraceptive efficacy is unlikely. Co-administration of this oral contraceptive did not influence the pharmacokinetics of Levetiracetam.

Digoxin

Levetiracetam (1000 mg twice daily) did not influence the pharmacokinetics and pharmacodynamics (ECG) of digoxin given as a 0.25 mg dose every day. Co-administration of digoxin did not influence the pharmacokinetics of Levetiracetam.

Warfarin

Levetiracetam (1000 mg twice daily) did not influence the pharmacokinetics of R and S warfarin. Prothrombin time was not affected by Levetiracetam. Co-administration of warfarin did not affect the pharmacokinetics of Levetiracetam.

Probenecid

Probenecid, a renal tubular secretion blocking agent, administered at a dose of 500 mg four times a day, did not change the pharmacokinetics of Levetiracetam 1000 mg twice daily. C^{ss}_{max} of the primary metabolite was approximately doubled in the presence of probenecid while the fraction of drug excreted unchanged in the urine remained the same. Renal clearance of the metabolite in the presence of probenecid decreased 60%, probably related to competitive inhibition of tubular secretion of this metabolite. The effect of Levetiracetam on probenecid was not studied.

WARNINGS

Suicidal Behavior And Ideation

Antiepileptic drugs (AEDs), including Levetiracetam, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 10 shows absolute and relative risk by indication for all evaluated AEDs.

Table 10: Risk By Indication For Antiepileptic Drugs In The Pooled Analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/ Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing Levetiracetam or any other AED must balance the risk of suicidal thoughts or behaviors with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Neuropsychiatric Adverse Events

Partial Onset Seizures

Adults

In adults experiencing partial onset seizures, Levetiracetam use is associated with the occurrence of central nervous system adverse events that can be classified into the following categories: somnolence and fatigue, coordination difficulties and behavioral abnormalities.

In controlled trials of adult patients with epilepsy experiencing partial onset seizures, 14.8% of Levetiracetam-treated patients reported somnolence, compared to 8.4% of placebo patients. There was no clear dose response up to 3000 mg/day. In a study where there was no titration, about 45% of patients receiving 4000 mg/day reported somnolence. The somnolence was considered serious in 0.3% of the treated patients, compared to 0% in the placebo group. About 3% of Levetiracetam-treated patients discontinued treatment due to somnolence, compared to 0.7% of placebo patients. In 1.4% of treated patients and in 0.9% of placebo patients the dose was reduced, while 0.3% of the treated patients were hospitalized due to somnolence.

In controlled trials of adult patients with epilepsy experiencing partial onset seizures, 14.7% of treated patients reported asthenia, compared to 9.1% of placebo patients. Treatment was discontinued in 0.8% of treated patients as compared to 0.5% of placebo patients. In 0.5% of treated patients and in 0.2% of placebo patients the dose was reduced.

A total of 3.4% of Levetiracetam-treated patients experienced coordination difficulties (reported as either ataxia, abnormal gait or incoordination) compared to 1.6% of placebo patients. A total of 0.4% of patients in controlled trials discontinued Levetiracetam treatment due to ataxia, compared to 0% of placebo patients. In 0.7% of treated patients and in 0.2% of placebo patients the dose was reduced due to coordination difficulties, while one of the treated patients was hospitalized due to worsening of pre-existing ataxia.

Somnolence, asthenia and coordination difficulties occurred most frequently within the first 4 weeks of treatment.

In controlled trials of patients with epilepsy experiencing partial onset seizures, 5 (0.7%) of Levetiracetam-treated patients experienced psychotic symptoms compared to 1 (0.2%) placebo patient. Two (0.3%) Levetiracetam-treated patients were hospitalized and their treatment was discontinued. Both events, reported as psychosis, developed within the first week of treatment and resolved within 1 to 2 weeks following treatment discontinuation. Two other events, reported as hallucinations, occurred after 1-5 months and resolved within 2-7 days while the patients remained on treatment. In one patient experiencing psychotic depression occurring within a month, symptoms resolved within 45 days while the patient continued treatment. A total of 13.3% of Levetiracetam patients experienced other behavioral symptoms (reported as aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, irritability, etc.) compared to 6.2% of placebo patients. Approximately half of these patients reported these events within the first 4 weeks. A total of 1.7% of treated patients discontinued treatment due to these events, compared to 0.2% of placebo patients. The treatment dose was reduced in 0.8% of treated patients and in 0.5% of placebo patients. A total of 0.8% of treated patients had a serious behavioral event (compared to 0.2% of placebo patients) and were hospitalized.

Pediatric Patients

In pediatric patients experiencing partial onset seizures, Levetiracetam is associated with somnolence, fatigue and behavioral abnormalities.

In the double-blind, controlled trial in children with epilepsy experiencing partial onset seizures, 22.8% of Levetiracetam-treated patients experienced somnolence, compared to 11.3% of placebo patients. The design of the study prevented accurately assessing dose-response effects. No patient discontinued treatment for somnolence. In about 3.0% of Levetiracetam-treated patients and in 3.1% of placebo patients the dose was reduced as a result of somnolence.

Asthenia was reported in 8.9% of Levetiracetam-treated patients, compared to 3.1% of placebo patients. No patient discontinued treatment for asthenia, but asthenia led to a dose reduction in 3.0% of Levetiracetam-treated patients compared to 0% of placebo patients.

A total of 37.6% of the Levetiracetam-treated patients experienced behavioral symptoms (reported as agitation, anxiety, apathy, depersonalization, depression, emotional lability, hostility, hyperkinesia, nervousness, neurosis and personality disorder), compared to 18.6% of placebo patients. Hostility was reported in 11.9% of Levetiracetam-treated patients, compared to 6.2% of placebo patients. Nervousness was reported in 9.9% of Levetiracetam-treated patients, compared to 2.1% of placebo patients. Depression was reported in 3.0% of Levetiracetam-treated patients, compared to 1.0% of placebo patients.

A total of 3.0% of Levetiracetam-treated patients discontinued treatment due to psychotic and nonpsychotic adverse events, compared to 4.1% of placebo patients. Overall, 10.9% of Levetiracetam-treated patients experienced behavioral symptoms associated with discontinuation or dose reduction, compared to 6.2% of placebo patients.

Myoclonic Seizures

During clinical development, the number of patients with myoclonic seizures exposed to Levetiracetam was considerably smaller than the number with partial seizures. Therefore, underreporting of certain adverse events was more likely to occur in the myoclonic seizure population. In adult and adolescent patients experiencing myoclonic seizures, Levetiracetam is associated with somnolence and behavioral abnormalities. It is expected that the events seen in partial seizure patients would occur in patients with JME.

In the double-blind, controlled trial in adults and adolescents with juvenile myoclonic epilepsy experiencing myoclonic seizures, 11.7% of Levetiracetam-treated patients experienced somnolence compared to 1.7% of placebo patients. No patient discontinued treatment as a result of somnolence. In 1.7% of Levetiracetam-treated patients and in 0% of placebo patients the dose was reduced as a result of somnolence.

Non-psychotic behavioral disorders (reported as aggression and irritability) occurred in 5% of the Levetiracetam-treated patients compared to 0% of placebo patients. Non-psychotic mood disorders (reported as depressed mood, depression and mood swings) occurred in 6.7% of Levetiracetam-treated patients compared to 3.3% of placebo patients. A total of 5.0% of Levetiracetam-treated patients had a reduction in dose or discontinued treatment due to behavioral or psychiatric events (reported as anxiety, depressed mood, depression, irritability and nervousness), compared to 1.7% of placebo patients.

Primary Generalized Tonic-Clonic Seizures

During clinical development, the number of patients with primary generalized tonic-clonic epilepsy exposed to Levetiracetam was considerably smaller than the number with partial epilepsy, described above. As in the partial seizure patients, behavioral symptoms appeared to be associated with Levetiracetam treatment. Gait disorders and somnolence were also described in the study in primary generalized seizures, but with no difference between placebo and Levetiracetam treatment groups and no appreciable discontinuations. Although it may be expected that drug related events seen in partial seizure patients would be seen in primary generalized epilepsy patients (e.g. somnolence and gait disturbance), these events may not have been observed because of the smaller sample size.

In patients 6 years of age and older experiencing primary generalized tonic-clonic seizures, Levetiracetam is associated with behavioral abnormalities.

In the double-blind, controlled trial in patients with idiopathic generalized epilepsy experiencing primary generalized tonic-clonic seizures, irritability was the most frequently reported psychiatric adverse event occurring in 6.3% of Levetiracetam-treated patients compared to 2.4% of placebo patients. Additionally, non-psychotic behavioral disorders (reported as abnormal behavior, aggression, conduct disorder and irritability) occurred in 11.4% of the Levetiracetam-treated patients compared to 3.6% of placebo patients. Of the Levetiracetam-treated patients experiencing non-psychotic behavioral disorders, one patient discontinued treatment due to aggression. Non-psychotic mood disorders (including anger, apathy, depression, mood altered, mood swings, negativism and tearfulness) occurred in 12.7% of Levetiracetam-treated patients compared to 8.3% of placebo patients. No Levetiracetam-treated patients discontinued or had a dose reduction as a result of these events. One patient experienced delusional behavior that required the lowering of the dose of Levetiracetam.

In a long-term open label study that examined patients with various forms of primary generalized epilepsy, along with the non-psychotic behavioral disorders, 2 of 192 patients studied exhibited psychotic-like behavior. Behavior in one case was characterized by auditory hallucinations and suicidal thoughts and led to Levetiracetam discontinuation. The other case was described as worsening of pre-existent schizophrenia and did not lead to drug discontinuation.

Withdrawal Seizures

Antiepileptic drugs, including Levetiracetam, should be withdrawn gradually to minimize the potential of increased seizure frequency.

PRECAUTIONS

Hematologic Abnormalities

Partial Onset Seizures

Adults

Minor, but statistically significant, decreases compared to placebo in total mean RBC count, mean hemoglobin and mean hematocrit were seen in Levetiracetam-treated patients in controlled trials.

A total of 3.2% of treated and 1.8% of placebo patients had at least one possibly significant (≤ 2.8 x 10^9/L) decreased WBC and 2.4% of treated and 1.4% of placebo patients had at least one possibly significant (≤ 1.0 x 10^9/L) decreased neutrophil count. Of the treated patients with a low neutrophil count, all but one rose towards or to baseline with continued treatment. No patient was discontinued secondary to low neutrophil counts.

Pediatric Patients

Minor, but statistically significant, decreases in WBC and neutrophil counts were seen in Levetiracetam-treated patients as compared to placebo. The mean decreases from baseline in the Levetiracetam-treated group were -0.4 x 10^9/L and -0.3 x 10^9/L, respectively, whereas there were small increases in the placebo group. Mean relative lymphocyte counts increased by 1.7% in Levetiracetam-treated patients, compared to a decrease of 4% in placebo patients (statistically significant).

In the well-controlled trial, more Levetiracetam-treated patients had a possibly clinically significant abnormally low WBC value (3.0% Levetiracetam-treated versus 0% placebo), however, there was no apparent difference between treatment groups with respect to neutrophil count (5.0% Levetiracetam-treated versus 4.2% placebo). No patient was discontinued secondary to low WBC or neutrophil counts.

Juvenile Myoclonic Epilepsy

Although there were no obvious hematologic abnormalities observed in patients with JME, the limited number of patients makes any conclusion tentative. The data from the partial seizure patients should be considered to be relevant for JME patients.

Hepatic Abnormalities

There were no meaningful changes in mean liver function tests (LFT) in controlled trials in adult or pediatric patients; lesser LFT abnormalities were similar in drug and placebo treated patients in controlled trials (1.4%). No adult or pediatric patients were discontinued from controlled trials for LFT abnormalities except for 1 (0.07%) adult epilepsy patient receiving open treatment.

Carcinogenesis, Mutagenesis, Impairment Of Fertility

Carcinogenesis

Rats were dosed with Levetiracetam in the diet for 104 weeks at doses of 50, 300 and 1800 mg/kg/day. The highest dose corresponds to 6 times the maximum recommended daily human dose (MRHD) of 3000 mg on a mg/m^2 basis and it also provided systemic exposure (AUC) approximately 6 times that achieved in humans receiving the MRHD. There was no evidence of carcinogenicity. A study was conducted in which mice received Levetiracetam in the diet for 80 weeks at doses of 60, 240 and 960 mg/kg/day (high dose is equivalent to 2 times the MRHD on a mg/m^2 or exposure basis). Although no evidence for carcinogenicity was seen, the potential for a carcinogenic response has not been fully evaluated in that species because adequate doses have not been studied.

Mutagenesis

Levetiracetam was not mutagenic in the Ames test or in mammalian cells *in vitro* in the Chinese hamster ovary/HGPRT locus assay. It was not clastogenic in an *in vitro* analysis of metaphase chromosomes obtained from Chinese hamster ovary cells or in an *in vivo* mouse micronucleus assay. The hydrolysis product and major human metabolite of Levetiracetam was not mutagenic in the Ames test or the *in vitro* mouse lymphoma assay.

Impairment Of Fertility

No adverse effects on male or female fertility or reproductive performance were observed in rats at doses up to 1800 mg/kg/day (approximately 6 times the maximum recommended human dose on a mg/m^2 or exposure basis).

Pregnancy

Pregnancy Category C

In animal studies, Levetiracetam produced evidence of developmental toxicity at doses similar to or greater than human therapeutic doses.

Administration to female rats throughout pregnancy and lactation was associated with increased incidences of minor fetal skeletal abnormalities and retarded offspring growth pre- and/or postnatally at doses ≥ 350 mg/kg/day (approximately equivalent to the maximum recommended human dose of 3000 mg [MRHD] on a mg/m^2 basis) and with increased pup mortality and offspring behavioral alterations at a dose of 1800 mg/kg/day (6 times the MRHD on a mg/m^2 basis). The developmental no effect dose was 70 mg/kg/day (0.2 times the MRHD on a mg/m^2 basis). There was no overt maternal toxicity at the doses used in this study.

Treatment of pregnant rabbits during the period of organogenesis resulted in increased embryofetal mortality and increased incidences of minor fetal skeletal abnormalities at doses ≥ 600 mg/kg/day (approximately 4 times MRHD on a mg/m^2 basis) and in decreased fetal weights and increased incidences of fetal malformations at a dose of 1800 mg/kg/day (12 times the MRHD on a mg/m^2 basis). The developmental no effect dose was 200 mg/kg/day (1.3 times the MRHD on a mg/m^2 basis). Maternal toxicity was also observed at 1800 mg/kg/day.

When pregnant rats were treated during the period of organogenesis, fetal weights were decreased and the incidence of fetal skeletal variations was increased at a dose of 3600 mg/kg/day (12 times the MRHD). 1200 mg/kg/day (4 times the MRHD) was a developmental no effect dose. There was no evidence of maternal toxicity in this study.

Treatment of rats during the last third of gestation and throughout lactation produced no adverse developmental or maternal effects at doses of up to 1800 mg/kg/day (6 times the MRHD on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Levetiracetam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Levetiracetam is excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants from Levetiracetam, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in patients below 4 years of age have not been established.

Geriatric Use

Of the total number of subjects in clinical studies of Levetiracetam, 347 were 65 and over. No overall differences in safety were observed between these subjects and younger subjects. There were insufficient numbers of elderly subjects in controlled trials of epilepsy to adequately assess the effectiveness of Levetiracetam in these patients.

A study in 16 elderly subjects (age 61-88 years) with oral administration of single dose and multiple twice-daily doses for 10 days showed no pharmacokinetic differences related to age alone.

Levetiracetam is known to be substantially excreted by the kidney and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function.

Use In Patients With Impaired Renal Function

Clearance of Levetiracetam is decreased in patients with renal impairment and is correlated with creatinine clearance. Caution should be taken in dosing patients with moderate and severe renal impairment and in patients undergoing hemodialysis. The dosage should be reduced in patients with impaired renal function receiving Zitera® and supplemental doses should be given to patients after dialysis.

OVERDOSE

Signs, Symptoms And Laboratory Findings Of Acute Overdosage In Humans

The highest known dose of Levetiracetam received in the clinical development program was 6000 mg/day. Other than drowsiness, there were no adverse events in the few known cases of overdose in clinical trials. Cases of somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with Levetiracetam overdoses in postmarketing use.

Treatment Or Management Of Overdose

There is no specific antidote for overdose with Levetiracetam. If indicated, elimination of unabsorbed drug should be attempted by emesis or gastric lavage; usual precautions should be observed to maintain airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the patient's clinical status.

Hemodialysis

Standard hemodialysis procedures result in significant clearance of Levetiracetam (approximately 50% in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to Levetiracetam or any of the inactive ingredients in Zitera® tablets.

PRESENTATION

Zitera® 500 mg tablets are yellow, oblong-shaped, scored, film-coated tablets engraved with "ALG Ž 500".

Zitera® 1000 mg tablets are white, oblong-shaped, scored, film-coated tablets engraved with "ALG Ž 1000".

Zitera® 500 mg and 1000 mg are available each in blister packs of 60 tablets.

Not all presentations may be marketed.

STORAGE

Store in a dry place below 25°C, protected from light. Do not refrigerate.

KEEP MEDICAMENT OUT OF REACH OF CHILDREN.

Do not exceed the prescribed dose.

Do not use after expiry date.

This is a medicament

- A medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold you the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

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